

## WHAT IS CLAIMED IS:

1. A method for producing a heterodimeric protein having bone stimulating activity comprising culturing a selected host cell containing a sequence 5 encoding a first selected BMP or fragment thereof and a sequence encoding a second selected BMP or fragment thereof, said sequences each being under the control of a suitable regulatory sequence capable of directing co-expression of said proteins, and isolating said heterodimeric protein from 10 the culture medium.

2. The method according to claim 1 wherein said first BMP or fragment thereof is present on a first vector transfected into said host cell and said second BMP or fragment thereof is present on a second vector transfected 15 into said host cell.

3. The method according to claim 1 wherein both said BMPs or fragments thereof are incorporated into a chromosome of said host cell.

20 4. The method according to claim 1 wherein both BMPs or fragments thereof are present on a single vector.

5. The method according to claim 2 wherein more than a single copy of the gene encoding each said BMP or fragment thereof is present on each vector.

6. The method according to claim 1 wherein said host cell is a hybrid cell prepared by culturing two fused selected, stable host cells, each host cell transfected with a sequence encoding a selected first or second BMP or fragment thereof, said sequences under the control of a suitable regulatory sequence capable of directing expression of each protein or fragment.

7. The method according to claim 1 wherein said host cell is a mammalian cell.

8. The method according to claim 1 wherein said host cell is an insect cell.

15 9. The method according to claim 1 wherein said host cell is a yeast cell.

10. A method for producing a heterodimeric protein having bone stimulating activity in a bacterial cell comprising culturing a selected host cell containing a sequence encoding a first selected BMP or fragment thereof

under the control of a suitable regulatory sequence capable  
of directing expression of the protein or protein fragment  
under conditions suitable for the formation of a soluble,  
monomeric protein; culturing a selected host cell containing  
5 a sequence encoding a second selected BMP or fragment  
thereof under the control of a suitable regulatory sequence  
capable of directing expression of the protein or protein  
fragment under said conditions to form a second soluble,  
monomeric protein; and mixing said soluble monomeric  
proteins under conditions permitting the formation of  
10 dimeric proteins associated by at least one covalent  
disulfide bond; isolating from the mixture a heterodimeric  
protein.

11. The method according to claim 10 wherein said  
15 host cell is E. coli.

12. The method according to claim 10 wherein said  
conditions comprise treating said protein with a  
solubilizing agent.

13. A recombinant heterodimeric protein having  
20 bone stimulating activity comprising a first protein or  
fragment of BMP-2 in association with a second protein or  
fragment thereof selected from the group consisting of BMP-

5, BMP-6, BMP-7 and BMP-8.

14. The protein according to claim 13 wherein  
said second protein is BMP-5.

5 15. The protein according to claim 13 wherein  
said second protein is BMP-6.

16. The protein according to claim 13 wherein  
said second protein is BMP-7.

17. The protein according to claim 13 wherein  
said second protein is BMP-8.

10 18. A recombinant heterodimeric protein having  
bone stimulating activity comprising a protein or fragment  
of BMP-4 in association with a second protein or fragment  
thereof selected from the group consisting of BMP-5, BMP-6,  
BMP-7 and BMP-8.

15 19. The protein according to claim 18 wherein  
said second protein is BMP-5.

20. The protein according to claim 18 wherein  
said second protein is BMP-6.

21. The protein according to claim 18 wherein  
said second protein is BMP-7.

22. The protein according to claim 18 wherein  
said second protein is BMP-8.

5           23. A recombinant heterodimeric protein having  
bone stimulating activity comprising a protein or fragment  
of a first BMP in association with a second protein or  
fragment of a second BMP produced by co-expressing said  
proteins in a selected host cell.

10          24. The protein according to claim 23 wherein  
said first BMP is BMP-2 and said second BMP is BMP-7.

15          25. A cell line comprising a nucleotide sequence  
encoding a first BMP or fragment thereof under control of a  
suitable expression regulatory system and a nucleotide  
sequence encoding a second BMP or fragment thereof under  
control of a suitable expression regulatory system, said  
regulatory systems capable of directing the co-expression of  
said BMPs or fragments thereof and the formation of  
heterodimeric protein.

20          26. The cell line according to claim 25 wherein

said nucleotide sequences encoding said first and second BMP proteins are present in a single DNA molecule.

27. The cell line according to claim 25 wherein  
said nucleotide sequence encoding said first BMP is present  
on a first DNA molecule and said nucleotide sequence  
encoding said second BMP is present on a second DNA  
molecule.

28. The cell line according to claim 26 wherein  
said single DNA molecule comprises a first transcription  
unit containing a gene encoding a first BMP or fragment  
thereof and a second transcription unit containing a gene  
encoding a second BMP or fragment thereof.

29. The cell line according to claim 26 wherein  
said single DNA molecule comprises a single transcription  
unit containing multiple copies of said gene encoding said  
first BMP or fragments thereof and multiple copies of said  
gene encoding said second BMP or fragments thereof.

30. A DNA molecule comprising a sequence encoding  
a first selected BMP or fragment thereof and a sequence  
encoding a second selected BMP or fragment thereof, said  
sequences under the control of at least one suitable

regulatory sequence capable of directing co-expression of each BMP or fragment thereof.

5           31. The molecule according to claim 30 comprising a first transcription unit containing a gene encoding a first BMP or fragment thereof and a second transcription unit containing a gene encoding a second BMP or fragment thereof.

10          32. The molecule according to claim 30 comprising a single transcription unit containing multiple copies of said gene encoding said first BMP or fragments thereof and multiple copies of said gene encoding said second BMP or fragments thereof.

15          33. The protein according to claim 23 wherein said first BMP is BMP-2 and said second BMP is BMP-6.

34. A recombinant BMP-2 homodimer having bone stimulating activity said homodimer produced in E. coli.

20          35. A method for producing a homodimeric BMP-2 protein having bone stimulating activity said method comprising culturing E. coli host cells and isolating and purifying said protein from the resulting culture medium.

36. A recombinant heterodimeric protein having  
bone stimulating activity comprising a first protein or  
fragment of BMP-2 in association with a second protein or  
fragment of BMP-2.